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Prevalence and Prognostic Significance of Left Ventricular Reverse Remodeling in Dilated Cardiomyopathy Receiving Tailored Medical Treatment

Marco Merlo, MD,* Stylianos A. Pyxaras, MD,* Bruno Pinamonti, MD,* Giulia Barbati, PHD,† Andrea Di Lenarda, MD,‡ Gianfranco Sinagra, MD*

Trieste and Padua, Italy

Objectives The purpose of this study was to determine the prevalence and prognostic role of left ventricular reverse remodeling (LVRR) in idiopathic dilated cardiomyopathy (IDCM).

Background Tailored medical therapy can lead to LVRR in IDCM. The prevalence and prognostic impact of LVRR remain unclear.

Methods We consecutively enrolled 361 IDCM patients. LVRR was defined as a left ventricular ejection fraction increase of ≥10 U or a left ventricular ejection fraction of ≥50% and a decrease in indexed left ventricular end-diastolic diameter of ≥10% or indexed left ventricular end-diastolic diameter of ≥33 mm/m^2 at 24 months (range 9 to 36 months). Follow-up echocardiographic data were available for 242 patients (67%), 34 (9%) died/underwent heart transplantation (HTx) before re-evaluation, and 85 (24%) did not have a complete re-evaluation. After re-evaluation, the surviving patients were followed for 110 ± 53 months; there were 55 deaths (23%) and 32 HTx (13%).

Results LVRR was found in 89 of 242 patients (37%). Baseline predictors of LVRR were higher systolic blood pressure ($p = 0.047$) and the absence of left bundle branch block ($p = 0.009$). When added to a prognostic baseline model including male sex, heart failure duration, New York Heart Association functional classes III to IV, LVEF, significant mitral regurgitation, and beta-blockers, LVRR, New York Heart Association functional classes III to IV, and significant mitral regurgitation after 24 months emerged as independent predictors of death/HTx and heart failure death/HTx. The model including follow-up variables showed additional prognostic power with respect to baseline model (for death/HTx, area under the curve: 0.80 vs. 0.70, respectively, $p = 0.004$). Furthermore, only LVRR was significantly associated with sudden death/major ventricular arrhythmia in the long-term.

Conclusions LVRR characterized approximately one-third of IDCM patients surviving 2 years while receiving optimal medical therapy and allowed a more accurate long-term prognostic stratification of the disease. (J Am Coll Cardiol 2011;57:1468–76) © 2011 by the American College of Cardiology Foundation

Dilated cardiomyopathy is a myocardial disease characterized by left ventricular dilation and systolic dysfunction that commonly result in heart failure (HF) (1,2). In the majority of patients, an etiological basis cannot be identified, and the patient is referred to as having an idiopathic dilated cardiomyopathy (IDCM) (3,4). IDCM has an incidence of >36.5 cases per 100,000 persons (5), and it accounts for nearly 50,000 hospitalizations and 10,000 deaths each year in the United States (6). The long-term prognosis of the disease has improved remarkably during the past 20 years (7,8). However, despite recent and continuous progress in drug treatment and, where applicable, cardiac resynchronization therapy (CRT), IDCM still remains the most common reason for heart transplantation (HTx) in adults and children (9,10).

See page 1477

Cardiac remodeling can be defined as genome expression, molecular, cellular, and interstitial changes that are manifested clinically as changes in size, shape, and function of the heart after cardiac injury (4,11). This phenomenon characterizes the natural history of IDCM (4,7,8). Furthermore, several authors over the past decade have suggested that in some IDCM patients, particularly those receiving tailored neurohormonal medical treatment (12–17), the left ventricle could undergo a reverse remodeling (left ventricular reverse remodeling [LVRR]), characterized by a decrease

From the *Cardiovascular Department, "Ospedali Riuniti" and University of Trieste, Trieste, Italy; †Department of Environmental Medicine and Public Health, University of Padua, Padua, Italy; and the ‡Cardiovascular Center, Azienda per i Servizi Sanitari (A.S.S.) n 1, Trieste, Italy. The authors have reported that they have no relationships to disclose.

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in dimensions and the normalization of shape associated with a significant improvement of pump function. Identification of LVRR could potentially add prognostic value for the stratification of long-term risk, whether or not associated with an improvement of symptoms. Nevertheless, there are no studies focused on early identification of clinical characteristics of this particular subgroup of IDCM patients in the literature and in particular the impact of early diagnosis and pharmacological treatment on LVRR and its long-term prognostic role.

Therefore, the objectives of the present study were to determine the prevalence of LVRR in IDCM patients receiving tailored medical therapy and to assess the clinical and laboratory predictors of LVRR and its prognostic role in long-term follow-up.

Methods

Study population. From 1988 to 1997, 361 consecutive patients with IDCM were enrolled in this study; they are part of the Heart Muscle Disease Registry of Trieste, a database of a tertiary referral center on cardiomyopathies. The end of follow-up was considered to be December 31, 2007, the date of death, or HTx. This study population had a potential clinical follow-up of at least 10 years. An IDCM diagnosis was defined according to the World Health Organization criteria (1). Informed consent was obtained from all subjects under the institutional review board policies of the Trieste hospital administration.

At enrollment, after obtaining an accurate clinical history, all patients underwent a physical examination, blood sampling for laboratory tests, 12-lead electrocardiography, standard chest X-ray, 24-h Holter monitoring, a complete echocardiographic and Doppler evaluation, exercise testing, and coronary angiography.

Until 1996, patients routinely underwent endomyocardial biopsy to exclude active myocarditis (according to the Dallas criteria) (18). Thereafter, a biopsy was performed only on patients with recent-onset HF and/or a clinical history suggesting active myocarditis.

The patients underwent a structured follow-up evaluation at the Cardiomyopathy Clinic of the Cardiovascular Department of Trieste. For the purpose of the study, we analyzed 242 of 361 patients (67%) with available clinical and echocardiographic data at baseline evaluation and at mid-term follow-up (mean 24 ± 7 months, range 9 to 36 months) receiving tailored medical treatment.

Regarding treatment, following our protocol, all patients enrolled in our study were treated with beta-blockers (metoprolol tartrate and later carvedilol) where appropriate, always following careful clinical stabilization on the optimal dose of angiotensin-converting enzyme (ACE) inhibitors, in addition to digitalis and diuretics, as clinically indicated. Daily doses of ACE inhibitors and beta-blockers are reported as equivalent of enalapril and carvedilol, respectively (enalapril equivalent doses: captopril, 7.5; lisinopril, 1; carvedilol equivalent doses: metoprolol, 2) (19) and refer to the end of titration period (generally 1 to 3 months after enrollment).

Moreover, from 1998 onward, after the preliminary data from our registry and the results of some trials on secondary prevention of sudden death (SD) (20–22), the use of an implantable cardioverter-defibrillator (ICD) for primary prevention began to take place in IDCM patients matching high-risk criteria for SD (persistent left ventricular ejection fraction [LVEF]) ≤35% and New York Heart Association functional classes II to III despite long-term optimal treatment) (23–25). No CRT was used in our population at mid-term follow-up.

Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
CRT = cardiac resynchronization therapy
HF = heart failure
HTx = heart transplantation
ICD = implantable cardioverter-defibrillator
IDCM = idiopathic dilated cardiomyopathy
LBBB = left bundle branch block
LVEF = left ventricular ejection fraction
LVRR = left ventricular reverse remodeling
MVA = major ventricular arrhythmia
NYHA = New York Heart Association
SD = sudden death

Echocardiographic study. Conventional M-mode, 2-dimensional, and Doppler variables were measured in all patients according to international guidelines. Left ventricular diameters were measured at M-mode and volumes, and LVEFs were calculated at 2-dimensional echocardiography from an apical 4-chamber view using the biplane method of disks. Right ventricular areas and fractional area contraction, as well as the end-systolic left atrial area, were also measured using the same approach. Mitral regurgitation was semiquantitatively graded considering the regurgitant jet area at color Doppler imaging (26). Mitral regurgitation with jet area >4 cm^2 was considered significant. The transmitral flow velocity curve was obtained by pulsed Doppler imaging, positioning the sample volume between the tips of the mitral leaflets. E- and A-wave peak velocities, E-wave deceleration time, and the ratio of early transmitral flow velocity to atrial flow velocity were measured, as described previously (20,26). The left ventricular filling pattern was classified as restrictive in the presence of an E-wave deceleration time <120 ms or a ratio of early transmitral flow velocity to atrial flow velocity ≥2 associated with an E-wave deceleration time ≤150 ms (27); for patients in atrial fibrillation, only E-wave data were considered.

All measurements were obtained from the mean of 3 beats for the patients with sinus rhythm, and 5 beats for those with atrial fibrillation. Chamber diameters, areas, and volumes were normalized for body surface area.

Reproducibility of Doppler echocardiographic data was previously published by our group (28).

Study design. LVRR was defined as the combined presence at mid-term follow-up of: 1) an increase in LVEF of at least 10 points or a follow-up LVEF ≥50% (in patients with an LVEF of 45% to 49% at enrollment); and 2) a decrease in indexed left ventricular end-diastolic diameter of at least

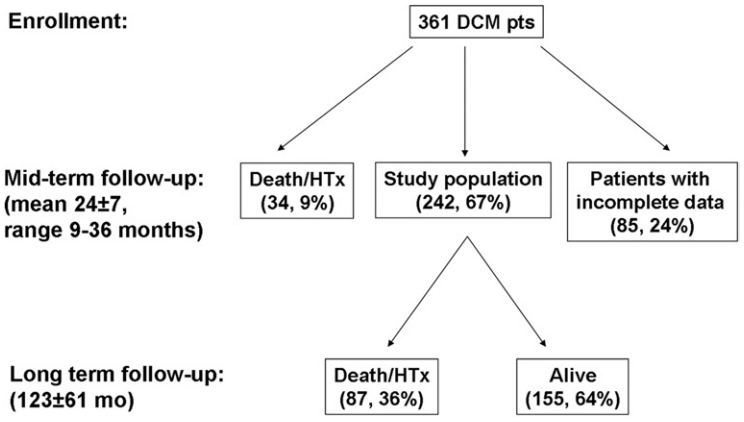

Figure 1 Follow-Up of Idiopathic Dilated Cardiomyopathy Study Population

HTx = heart transplantation; mo = months; pts = patients.

10% or an indexed left ventricular end-diastolic diameter ≤33 mm/m^2 (29).

The primary prognostic end point was considered death or HTx. The indication for HTx was considered in patients with refractory HF requiring inotropic treatment and/or mechanical support (status I) (30).

Two secondary combined clinical end points were considered: 1) HF death/HTx and 2) SD and major ventricular arrhythmias (MVAs). SD was defined as an immediate death or a death occurring within 1 h after the onset of symptoms or during sleep in stable NYHA functional class I to III patients. As MVAs were considered ventricular fibrillation/flutter or a sustained ventricular tachycardia (hemodynamically unstable or lasting more than 30 s) or appropriate ICD intervention.

Information regarding the end points was obtained directly from the patient, from his or her physician, or from the registers of death of the municipalities of residence. This study was performed in accordance with the guidelines set by the Declaration of Helsinki (31) and with the local legal requirements.

Statistical analysis. All values are reported as mean ± SD or percentages. Continuous variables were compared between groups by analysis of variance, whereas for binary variables, the chi-square test was used by applying Yates correction for continuity when necessary. To predict LVRR from baseline variables, first a univariate screening of all clinical-laboratory parameters of patients at enrollment was made (estimating univariable logistic regression models variable by variable); then to estimate the multivariable logistic regression equation, a stepwise backward conditional algorithm was applied to the list of selected parameters (i.e., with $p < 0.1$) at the univariate procedure. Survival curves were calculated according to the Kaplan-Meier method, and the comparison between curves was carried out with the log-rank test.

Two prognostic survival models were compared by means of the Cox hazard proportional analysis: model 1, which included clinical-laboratory data at baseline evaluation (male sex, HF duration, NYHA functional classes III to IV, LVEF, moderate to severe mitral regurgitation, treatment with beta-blockers), selected by means of a backward conditional stepwise procedure, and model 2, which also incorporated the presence of LVRR, NYHA functional classes III to IV, and moderate to severe mitral regurgitation at mid-term follow-up. The prognostic accuracy of the 2 models and the possible additive prognostic role of the model 2 with respect to the sole model 1 were evaluated by using receiver-operating characteristic analysis.

All results were considered statistically significant when $p < 0.05$. The entire analysis was performed using the SPSS package, version 14.0 (SPSS Inc., Chicago, Illinois) and R statistical software version 2.5 (32).

Results

Clinical and echocardiographic data were available for 242 of 361 patients (67%) at mid-term follow-up (24 ± 7 months, range 9 to 36 months) (Fig. 1). After the mid-term evaluation, the surviving patients were followed for a mean follow-up of 110 ± 53 months; there were 55 deaths and 32 HTx.

The clinical and laboratory findings of these patients at the first evaluation are summarized in Table 1. Our patients were predominantly males (74%). The mean age at diagnosis was 43 ± 13 years. A family pattern was identified in 26% of cases. HF duration before diagnosis was 13 ± 25 months. Less than one-fourth of our population belonged to NYHA functional classes III to IV at baseline (18%). The electrocardiogram showed a complete left bundle branch block (LBBB) in 32% of patients. The echocardiographic

Table 1 Baseline Characteristics of the Study Population (n = 242)

Age, yrs	43 ± 13
Males	74
Familial IDCM	26
Duration of HF, months	13 ± 25
SBP, mm Hg	124 ± 14
DBP, mm Hg	79 ± 10
NYHA functional class III to IV	18
Serum hemoglobin, g/dl	14 ± 1.5
Serum creatinine, mg/dl	1.1 ± 0.2
Sinus rhythm	94
LBBB	32
LVEF, %	31 ± 10
LVEF ≤30%	50
LVEDDI, mm/m^2	37 ± 5
LVESDI, mm/m^2	31 ± 6
LVEDVI, ml/m^2	106 ± 39
LVESVI, ml/m^2	75 ± 35
Restrictive filling pattern	24
Significant MR	34
Beta-blockers	85
Carvedilol equivalent dose, mg/day	57 ± 25
ACE inhibitors/sartans	91
Enalapril equivalent dose, mg/day	22 ± 12
Diuretics	53
Digitalis	78
Amiodarone	23

Values are mean ± SD or %.

ACE = angiotensin-converting enzyme; DBP = diastolic blood pressure; HF = heart failure; IDCM = idiopathic dilated cardiomyopathy; LBBB = left bundle branch block; LVEDDI = left ventricular end-diastolic diameter index; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESDI = left ventricular end-systolic diameter index; LVESVI = left ventricular end-systolic volume index; MR = mitral regurgitation; NYHA = New York Heart Association; SBP = systolic blood pressure.

evaluation at baseline was consistent with a severe reduction of systolic function (LVEF 31 ± 10%) and with a moderate left ventricular dilation (indexed end-diastolic diameter: 37 ± 5 mm/m^2). A restrictive filling pattern was found in 24% of our population, and significant mitral regurgitation in 34%. Neurohormonal drug treatment with ACE inhibitors and beta-blockers was tailored in the majority of patients (91% and 85%, respectively) at target doses. Eighty-five patients (24%) had not undergone a complete noninvasive evaluation at mid-term follow-up. Most of clinical-laboratory features of this group of patients, including left ventricular shape, were not different from those of the study population, except that they were older with relatively higher blood pressure and more frequent atrial fibrillation (Table 2). Initially, they were less intensively treated with beta-blockers, and then they were followed at other centers. The long-term survival curves were not different from those of the study population (data not shown).

Thirty-four patients (9%) achieved the primary end point (death/HTx) before this follow-up visit (7 [2%] HF deaths; 15 [4%] urgent HTx; 11 [3%] SD). As expected, patients who achieved the primary end point were characterized at

Table 2 Comparison of Baseline Clinical-Laboratory Features Between Study Population and Patients With Incomplete Noninvasive Re-Evaluation at Mid-Term Follow-Up

	Noninvasive Re-Evaluation		
	Incomplete (n = 85)	Complete (n = 242)	p Value
Age, yrs	49 ± 14	43 ± 13	0.002
Male	70	74	NS
HF duration, months	12 ± 21	13 ± 25	NS
Familial IDCM	21	26	NS
SBP, mm Hg	129 ± 18	124 ± 14	0.008
NYHA functional class III to IV	20	18	NS
GFR ≤60 ml/min	17	11	NS
Sinus rhythm	86	94	0.022
LBBB	33	32	NS
LVEF, %	31 ± 7	31 ± 10	NS
LVEDDI, mm/m^2	36 ± 5	37 ± 5	NS
LVEDVI, ml/m^2	101 ± 37	106 ± 39	NS
Restrictive filling pattern	25	24	NS
Significant MR	39	34	NS
ACE inhibitors/sartans	93	91	NS
Beta-blockers	68	85	0.001
Diuretics	61	53	NS
Digitalis	79	78	NS

Values are mean ± SD or %.

GFR = glomerular filtration rate; other abbreviations as in Table 1.

baseline by more severe and advanced disease with respect to the remaining patients (data not shown).

At mid-term follow-up, LVRR was found in 89 of 242 patients analyzed (37%). At baseline, patients with LVRR showed lower LVEF (28 ± 8% vs. 33 ± 8%, $p < 0.001$) and a higher rate of a left ventricular restrictive filling pattern (42% vs. 15%, $p = 0.004$) with respect to the others. No other significant differences were documented (data not shown).

At logistic regression analysis (Table 3), baseline systolic blood pressure (for every 10-mm Hg increase: odds ratio: 1.23, 95% confidence interval: 1.01 to 1.53; $p = 0.047$) and the absence of LBBB (odds ratio: 2.47, 95% confidence interval: 1.25 to 4.87; $p = 0.009$) resulted as independent predictors of LVRR (univariate odds ratios are reported in Online Table 1).

The survival curves of the study population classified according to LVRR are shown in Figure 2. IDCM patients with LVRR had a significantly better long-term prognosis with respect to the others ($p < 0.001$). The HTx-free survival rates were, respectively, 94%, 85%, and 78% versus

Table 3 Baseline Independent Predictors of LVRR at Mid-Term Follow-Up

	OR	95% CI	p Value
SBP, per 10-mm Hg increase	1.23	1.01–1.53	0.047
Absence of LBBB	2.47	1.25–4.87	0.009

CI = confidence interval; LVRR = left ventricular reverse remodeling; OR = odds ratio; other abbreviations as in Table 1.

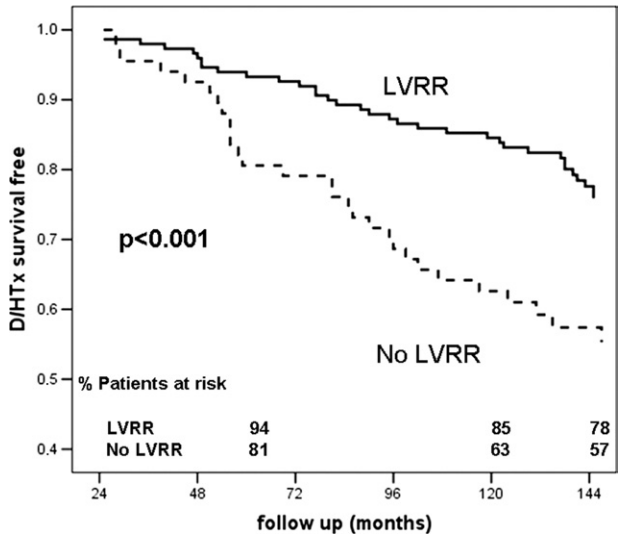

Figure 2 Long-Term Prognostic Impact of LVRR in Idiopathic Dilated Cardiomyopathy Patients

Comparison of long-term heart transplantation (HTx)-free survival curves between left ventricular reverse remodeling (LVRR) and non-LVRR patient subgroups. Note that the starting time point is 24 months (range 9 to 36 months). D = death.

81%, 63%, and 57% at 5, 10, and 12 years of follow-up in patients with and without LVRR.

The event rates of the patients with LVRR with respect to the other patients are shown in Table 4. LVRR proved to be associated with a lower rate of HF death/HTx (6% vs. 27%, p = 0.005), and SD/MVA (16% vs. 29%, p = 0.022).

Baseline prognostic independent predictors (model 1) for death/HTx, HF death/HTx, and SD/MVA are shown in Table 5 (univariate hazard ratios are reported in Online Table 2). Table 6 shows the prognostic role of model 1 and model 2 (which included LVRR, NYHA functional classes III to IV and moderate to severe mitral regurgitation at mid-term follow-up) both for predicting primary and secondary end points. LVRR resulted significantly predictive for HTx-free survival (hazard ratio: 0.44, 95% confidence interval: 0.25 to 0.78; p = 0.005), independently from other follow-up parameters. Similar results were also obtained with this model for prediction of the secondary end points, differently from NYHA functional classes III to IV and moderate to severe mitral regurgitation at mid-term follow-up that were not protective against SD/MVA in the long term.

Table 5 Baseline Prognostic Model (Model 1)

	HR	95% CI	p Value	AUC
Death/HTx				
Male	1.72	1.11–2.64	0.01	
HF duration (per 12-month increase)	1.13	1.05–1.21	<0.001	
NYHA functional class III to IV	1.68	1.12–2.50	0.01	0.70
LVEF (per 10-U decrease)	1.35	1.11–1.64	0.002	
Moderate to severe MR	1.52	1.04–2.23	0.03	
Beta-blockers	0.46	0.31–0.68	<0.001	
Pump failure death/HTx				
HF duration (per 12-month increase)	1.12	1.02–1.23	0.01	
NYHA functional class III to IV	1.78	1.00–3.19	0.05	0.68
Moderate to severe MR	2.51	1.37–4.59	0.003	
Beta-blockers	0.44	0.25–0.77	0.004	
Sudden death/MVA				
HF duration (per 12-month increase)	1.11	1.01–1.22	0.03	
LVEF (per 10-U decrease)	1.49	1.22–1.81	0.005	0.63

AUC = area under the curve; HR = hazard ratio; other abbreviations as in Tables 1, 3, and 4.

The accuracy comparison between the 2 models is shown in the receiver-operating characteristic curves (Fig. 3). The incremental prognostic power of model 2 versus model 1 is demonstrated both for death/HTx (area under the curve: 0.80 vs. 0.70, respectively; p = 0.004) and for HF death/HTx (area under the curve: 0.77 vs. 0.68, respectively; p = 0.002). A trend toward statistical significance was shown also for SD/MVA (area under the curve: 0.69 vs. 0.63, respectively; p = 0.1). Similar results were obtained by repeating the analysis, censoring heart transplant recipients (data not shown).

Discussion

The first main result of the present study is the observation that about one-third of our patients with IDCM surviving 2 years showed an LVRR at mid-term follow-up on tailored medical therapy. To the best of our knowledge, this is the first study that analyzes LVRR in a large population of patients with IDCM enrolled in a tertiary center and followed for at least 10 years. On the other hand, our data are in keeping with those in the literature concerning HF in general, showing that treatment with drugs capable of

Table 4 Events in the Patients With LVRR at Mid-Term Follow-Up Compared With the Other Patients on Long-Term Follow-Up*

Type of Event	All Patients n = 242	LVRR n = 89 (37%)	No LVRR n = 153 (63%)	p Value
Overall death/HTx	87 (36)	17 (19)	70 (46)	<0.001
Cardiovascular death	51 (21)	9 (10)	42 (27)	<0.001
HF death/HTx	47 (19)	5 (6)	42 (27)	0.005
Sudden death/MVA	58 (24)	14 (16)	44 (29)	0.022

Values are n (%). *Long-term follow up was 123 ± 61 months.
HTx = heart transplantation; MVA = major ventricular arrhythmia; other abbreviations as in Tables 1 and 3.

Table 6 Incremental Prognostic Role of LVRR, NYHA Functional Classes III to IV, and Moderate to Severe MR at Mid-Term Follow-Up (Model 2)

	HR	95% CI	p Value	AUC
Death/HTx				0.80
Model 1*	2.02	1.48–2.76	<0.001	
LVRR	0.44	0.25–0.78	0.005	
NYHA functional class III to IV at 24 months	3.75	2.03–6.95	<0.001	
Moderate to severe MR at 24 months	1.70	1.02–2.83	0.04	
Pump failure death/HTx				0.77
Model 1†	1.82	1.04–3.17	0.03	
LVRR	0.24	0.07–0.84	0.03	
NYHA functional class III to IV at 24 months	6.73	2.92–15.53	<0.001	
Moderate to severe MR at 24 months	2.79	1.22–6.34	0.01	
Sudden death/MVA				0.69
Model 1‡	2.18	1.49–3.19	<0.001	
LVRR	0.39	0.21–0.74	0.004	
NYHA functional class III to IV at 24 months	1.13	0.41–3.12	0.80	
Moderate to severe MR at 24 months	1.50	0.80–2.79	0.20	

*Model 1 includes baseline variables: male sex, HF duration, NYHA functional classes III to IV, LVEF, moderate to severe MR, and beta-blockers. †Model 1 includes baseline variables: HF duration, NYHA functional classes III to IV, moderate to severe MR, and beta-blockers. ‡Model 1 includes baseline variables: HF duration, and LVEF.

Abbreviations as in Tables 1, 3, 4, and 5.

antagonizing the neurohormonal system can lead to LVRR in patients with chronic HF and depressed LVEF secondary to multiple etiologies (12–17,33–35). Several hypotheses about the potential mechanisms of LVRR induced by drug therapy were postulated. First, the treatment of HF can influence the hemodynamics favorably by decreasing left ventricular pre-load and afterload. Moreover, recent studies have also suggested a direct action of beta-blockers on cardiac myocytes. In fact, patients with improvement of the LVEF with beta-blocker treatment were characterized by a concurrent increase in sarcoplasmic reticulum Ca^{2+} ATPase mRNA and alpha-myosin heavy chain mRNA, thus suggesting that left ventricular functional improvement was associated with favorable changes in myocardial gene expression (34).

In our study, a higher baseline systolic blood pressure and a lower prevalence of LBBB turned out to be independent predictors of LVRR. This may suggest a higher probability of improvement in patients with more chances of tailoring treatment and an increased possibility of modulating the afterload in the absence of severe, long-standing, irreversible structural abnormalities (7,8). This fact confirms the importance of an early diagnosis of the disease to achieve the maximum benefit from tailored neurohormonal treatment in terms of HF deaths/HTx and MVA prevention. However, it must be noted that LVRR could not be obtained in every single patient, and some patients died or underwent

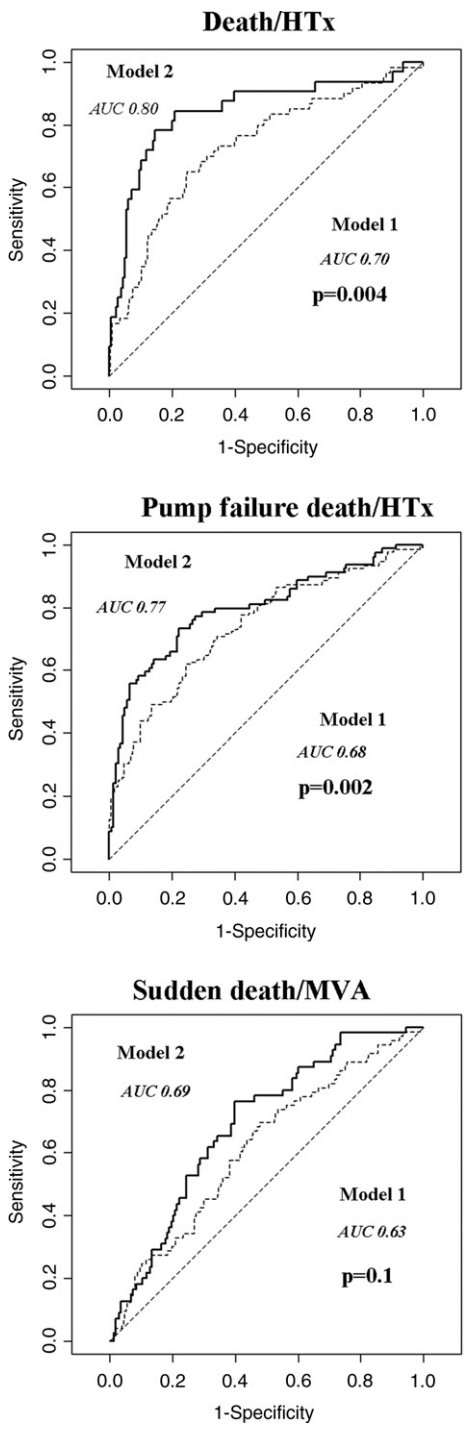

Figure 3 ROC Curves to Evaluate Accuracy of Model 2 Versus Model 1

Comparison of the receiver-operating characteristic (ROC) curves for prediction of events between the baseline model (model 1, **dashed line**) and the model containing left ventricular reverse remodeling, New York Heart Association functional class, and mitral regurgitation at mid-term follow-up (model 2, **solid line**). A significant improvement in accuracy is observed for model 2 in predicting death/heart transplantation (HTx) and pump failure death/HTx; a nonsignificant trend was observed for prediction of sudden death/major ventricular arrhythmia (MVA). AUC = area under the curve.

HTx within the first 24 months of follow-up. This patient subgroup presented a severe and advanced disease at diagnosis and needed early aggressive therapeutic therapy. Thus, the need emerges for very early identification of IDCM patients with a poor short-term prognosis to apply nonpharmacological therapies as soon as possible.

Long-term prognostic implications of LVRR. In our patients with IDCM, the evolution of LVRR at mid-term follow-up receiving tailored medical treatment predicted a lower rate of major (HTx is not a fatal event) cardiovascular events on long-term follow-up, independently from NYHA functional class and mitral regurgitation during follow-up. In fact, differently from NYHA functional classes III to IV and moderate to severe mitral regurgitation at mid-term follow-up, LVRR showed a significant independent protective prognostic role for death/HTx, HF death/HTX, and SD/MVA. On the other hand, NYHA functional classes III to IV and significant mitral regurgitation showed an independent prognostic role for death/HTx and HF death/HTx but not for SD/MVA.

As far as we know, there are no other studies reported in literature that evaluated the association between LVRR and major cardiovascular events in the long term in a large cohort of IDCM patients exclusively receiving tailored medical treatment. In a recent study, Yu et al. (36) showed a significant improvement in the survival rate of HF patients with LVRR; however, in that study, these results were achieved by CRT treatment, and the follow-up was relatively short (approximately 2 years).

Our data also demonstrated the improved accuracy of the prognostic model containing combined baseline and mid-term follow-up data, a key issue in the long-term management of IDCM. This underscores the importance not only of an accurate and complete initial diagnosis, but also of continuous, individualized follow-up with quantitative echocardiographic assessment and tailored drug treatment based on well-established clinical and laboratory data.

Clinical implications. This study underscores that about one-third of patients with IDCM shows a mid-term significant improvement of symptoms and LVRR on optimal tailored medical therapy. This group of patients had a favorable prognosis and was characterized at diagnosis by reversible myocardial damage despite severe hemodynamic impairment (LVRR patients presented a lower baseline LVEF and higher rate of a left ventricular restrictive filling pattern with respect to the others) and could tolerate a higher dose of ACE inhibitors and beta-blockers (LVRR group vs. others at 24 months, respectively: equivalent dose of enalapril 30 ± 13 mg/day vs. 24 ± 13 mg/day, $p = 0.001$; equivalent dose of carvedilol 73 ± 29 mg/day vs. 62 ± 33 mg/day, $p = 0.018$). This result highlights that, using LVRR, we could early identify a subgroup of patients with a benign prognosis among a population with a severe form of the disease.

Although the improvement of symptoms is already expressed after few months, reverse remodeling usually begins after 6 months, to be completed in 12 to 24 months. As a consequence, patients who express LVRR do not match any more class I indications for ICD or CRT implantation showing a long-term lower risk of major ventricular arrhythmias (37). However, some patients die earlier during the follow-up, sometimes suddenly. The timing of ICD and/or CRT implantation in IDCM is a critical issue. Although the guidelines suggest that an ICD can be indicated only in patients who are already receiving maximal medical therapy, it is not clear how the optimization of treatment can modify ICD indications and how safe it is to wait to optimize treatment before implanting an ICD. Patients with more advanced disease at diagnosis (the presence of LBBB, low systolic blood pressure), usually treated with a lower dose of ACE inhibitors and beta-blockers, with no significant improvement of symptoms and hemodynamics within 3 to 6 months, are associated with a lower probability of LVRR after 12 to 24 months and a higher risk of cardiovascular events, including sudden death. In these cases, it probably would not be safe to wait further without ICD/CRT implantation. Nevertheless, there is the need for further studies to recognize the patients in which early implantation of ICD and/or CRT are indicated.

LVRR was the unique follow-up parameter independently associated with SD/MVA in the long term. The improvement of HF symptoms and of mitral regurgitation emerged as predictors only for death/HTx and HF death/HTx. The present study underscores the importance not only of an accurate and complete initial diagnosis, but also of continuous, individualized follow-up on tailored drug treatment with quantitative echocardiographic assessment based on well-established clinical and laboratory data. From our results, there is not only a clear prognostic value of the complete left ventricular contractility and dimension restoration, but also a role for progressive improvement of left ventricular dysfunction and dilation during the mid-term follow-up for all the major cardiovascular events related to IDCM. Using LVRR, we could describe at the same time the dynamic process of clinical-laboratory improvement of IDCM patients receiving optimal medical treatment and the achievement of a target absolute value of LVEF. This issue represents a new finding that could be of great interest for the clinical cardiology community.

Finally, despite significant improvement of left ventricular function and remodeling at mid-term, long-term evolution of IDCM is actually not known. Because the possibility of long-term progressive remodeling also in patients with initial recovery of left ventricular function (38), continuous surveillance over time of the evolution of IDCM is therefore mandatory to identify those at higher risk and the correct timing of nonpharmacological interventions.

Study limitations. The current study population was enrolled in a tertiary referral center for cardiomyopathies and HF, thus imposing a selection bias with respect to the characteristics of IDCM in the general population.

In addition, 85 of the initial 361 patients did not have a complete noninvasive evaluation (including valuable echocardiographic data), decreasing the number of potential controls for analysis. Even if this group of patients had

similar clinical-laboratory characteristics (except that they were older with relatively higher blood pressure and more frequent atrial fibrillation) and similar long-term outcome compared with the study population, our prognostic models were obtained in patients with complete follow-up data and treated according to current evidence (i.e., with ACE inhibitors and beta-blockers in 90% of them) and should be applied only to this type of patient.

Furthermore, 34 of 361 patients (9%) died or underwent HTx before re-evaluation. We excluded these patients from our analysis because no complete clinical-laboratory data were available to classify them as non-LVRR; moreover, 11 of them died suddenly. This issue underscores the need for prognostic predictors of LVRR to apply early aggressive therapies (HTx, ICD, and/or CRT) in patients with an advanced and severe disease already at diagnosis. In the present study, LVRR was assessed by the combined presence at mid-term follow-up of a decrease in left ventricular dimensions and increase in LVEF.

Finally, we must note that despite the stepwise procedure used to find the most significant set of independent prognostic factors, in the case of the cause-specific end points of HF death/HTX and SD/MVA, an overfitting issue could be present because Cox models should be used with a minimum of 5 to 10 outcome events per predictor variable (39).

Conclusions

LVRR characterized about one-third of our IDCM population, alive at mid-term follow-up receiving tailored pharmacological treatment, and emerged as an independent predictor of long-term prognosis. The evolution to LVRR suggests less structural cardiac damage at the time of diagnosis and a higher probability of better response to treatment. Our study underscores the importance of considering clinical and laboratory data at baseline and during follow-up to improve the prognostic stratification of IDCM.

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Reprint requests and correspondence: Dr. Marco Merlo, Cardiovascular Department, Polo Cardiologico, Ospedale di Cattinara, University of Trieste, Via Valdoni 1, 34149 Trieste, Italy. E-mail: marco.merlo@hotmail.it.

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Key Words: idiopathic dilated cardiomyopathy ■ left ventricular reverse remodeling ■ prognosis ■ tailored medical treatment.

APPENDIX

For supplemental tables, please see online version of this article.